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Cardiovascular risk prediction using physical performance measures in COPD: results from a multicentre observational study

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ABSTRACT

Objectives Although cardiovascular disease (CVD) is a common comorbidity associated with chronic obstructive pulmonary disease (COPD), it is unknown how to improve prediction of cardiovascular (CV) risk in individuals with COPD. Traditional CV risk scores have been tested in different populations but not uniquely in COPD. The potential of alternative markers to improve CV risk prediction in individuals with COPD is unknown. We aimed to determine the predictive value of conventional CVD risk factors in COPD and to determine if additional markers improve prediction beyond conventional factors.

Design Data from the Evaluation of the Role of Inflammation in Chronic Airways disease cohort, which enrolled 729 individuals with Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage II–IV COPD were used. Linked hospital episode statistics and survival data were prospectively collected for a median 4.6 years of follow-up.

Setting Five UK centres interested in COPD.

Participants Population-based sample including 714 individuals with spirometry-defined COPD, smoked at least 10 pack years and who were clinically stable for >4 weeks.

Interventions Baseline measurements included aortic pulse wave velocity (aPWV), carotid intima–media thickness (CIMT), C reactive protein (CRP), fibrinogen, spirometry and Body mass index, airflow Obstruction, Dyspnoea and Exercise capacity (BODE) Index, 6 min walk test (6MWT) and 4 m gait speed (4MGS) test.

Primary and secondary outcome measures New occurrence (first event) of fatal or non-fatal hospitalised CVD, and all-cause and cause-specific mortality.

Results Out of 714 participants, 192 (27%) had CV hospitalisation and 6 died due to CVD. The overall CV risk model C-statistic was 0.689 (95% CI 0.688 to 0.691). aPWV and CIMT neither had an association with study outcome nor improved model prediction. CRP, fibrinogen, GOLD stage, BODE Index, 4MGS and 6MWT were associated with the outcome, independently of conventional risk factors ($p<0.05$ for all). However, only 6MWT improved model discrimination (C=0.727, 95% CI 0.726 to 0.728).

Conclusion Poor physical performance defined by the 6MWT improves prediction of CV hospitalisation in individuals with COPD.

Trial registration number ID 11101.

Strengths and limitations of this study

- This is the first study assessing the utility of conventional cardiovascular (CV) disease risk factors for CV risk prediction and the value of additional markers of risk within a chronic obstructive pulmonary disease (COPD) cohort.
- Patient-level cohort data were linked to hospital admission data (ie, hospital episode statistics) obtained from the National Health Services in England, Scotland and Wales, and Office for National Statistics record of mortality with analyses limited to 5 years of follow-up.
- Hospitalised CV episodes were coded based on International Statistical Classification of Diseases and Related Health Problems, 10th Revision, classifications extracted from both primary and secondary positions.
- A multivariable prediction model, with 10-fold cross validation and 200 replications, was used to evaluate a wide range of CV and physical performance biomarkers.
- Generalisability of our results is limited to those with moderate COPD in the UK with NHS hospitalisations.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is associated with a twofold to threefold increased risk of coronary artery disease and other cardiovascular (CV) comorbidities.[1 2] COPD and cardiovascular disease (CVD) are common conditions that share important common risk factors, such as smoking and physical inactivity, and both tend to affect older people. In addition,

both conditions are often associated with raised systemic inflammatory markers and increased arterial stiffness.[3 4]

Given the global healthcare burden associated with CVD,[5] there is incentive to improve the accuracy of CV risk prediction in different populations. Individuals with COPD may be considered constitutively at high CV risk, given their age and smoking history. However, it is unknown whether classic CV risk prediction models, such as the Framingham General CV Risk score, which predicts an individual's 10-year risk of developing CVD based on an algorithm of weighted risk factors and has been tested in a number of different populations,[6–9] perform well in individuals with COPD.[10 11]

Conceptually, the performance of the Framingham model might be improved by additional measures. Candidate measurements include surrogate CV risk markers that impart mechanistic information (ie, aortic pulse wave velocity (aPWV) or carotid intima–media thickness (CIMT)), inflammatory markers (ie, C reactive protein (CRP)) or measures of physical performance that enhance CV risk prediction in individuals with COPD. In fact, the value of these measures in CV risk prediction have been explored in different population groups. For example, the 6 min walk test (6MWT) significantly improved risk prediction in patients with stable coronary disease.[12] In individuals with intermediate CV risk but without CVD, adding CRP or fibrinogen to conventional risk factors modestly improved CV event prediction.[13] A meta-analysis of aPWV studied in different disease cohorts showed it improved CV event prediction independently of conventional risk factors.[14] In contrast, CIMT measurement, although associated with CV risk factors, did not significantly improve risk prediction beyond traditional factors in individuals with hypertension.[15] Given that individuals with COPD, in addition to having high CV risk based on conventional factors, also have increased aPWV, CIMT[4] and increased inflammatory markers,[16] as well as reduced lung function, which is associated with increased CV risk in the general population[17] and reduced physical performance,[18 19] the clinical significance of these findings in relation to CV risk prediction in individuals with COPD is an important question to address.

The aims of our study were to first determine the predictive value of conventional CVD risk factors for CV risk, defined by new occurrence (first event since study enrolment) of fatal or non-fatal hospitalised CVD in individuals with stable Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage II–IV[20] COPD. A secondary aim was to determine whether addition of alternative CV measures (ie, aPWV and CIMT), inflammatory markers (ie, CRP and fibrinogen), COPD severity (ie, GOLD stage and Body mass index (BMI), airflow Obstruction, Dyspnoea and Exercise capacity (BODE) Index), as well as physical performance tests commonly used in COPD research (ie, 6MWT and 4 m gait speed (4MGS)) improved the predictive value of a CV risk model based on conventional CVD risk factors for CV risk prediction. We addressed these questions in the Evaluation of the Role of Inflammation in Chronic Airways disease (ERICA) COPD cohort using study data and linked UK electronic health records.

METHODS

Study design and participants

The ERICA study is a multicentre, observational cohort study with 729 individuals with stable GOLD stage II–IV[20] COPD, established to identify important CV and physical performance biomarkers that could be targeted to improve the outcomes of individuals with COPD. Participants had a clinical diagnosis of COPD, smoking history of at least 10 pack years, postbronchodilator forced expiratory lung volume in one second (FEV_1)/forced vital capacity ratio of <0.7 and FEV_1 ≤80% of predicted normal lung function, and were aged >40 years old and clinically stable for >4 weeks. Full details of the protocol have been provided elsewhere.[21] Baseline data captured included demographics, spirometry, blood circulating biochemical markers, measures of arterial stiffness (ie, aPWV and Augmentation Index (AIx)), CIMT and physical performance (ie, 4MGS and 6MWT). Individuals in the ERICA study were linked with UK National Health Services (NHS) electronic healthcare records (ie, hospital episode statistics (HES) data are a database that includes details of all hospital admissions, accident and emergency department visits and outpatient appointments at an individual patient level)[22] and Office for National Statistics death data through anonymised identifications provided by the NHS.

Clinical measures

After 4 hours of fasting, with no bronchodilators for 6 hours, and 10 minutes of supine rest, carotid–femoral aPWV and AIx measurements were taken using a SphygmoCor system as previously described.[23] CIMT of the common carotid arteries was measured using B-mode ultrasound at a distance of 1 cm from the carotid bulb with a linear probe of 7–12 MHz.[24] The thickest artery of the two was included in the analysis. Fasting blood samples were taken for biochemical analysis, including plasma fibrinogen, serum CRP and glucose. Physical performance measures 6MWT[25] and 4MGS[26] were assessed according to guidelines. Diabetes status and antihypertensive treatment were self-reported at baseline study visit. Disease severity was defined according to GOLD classification.[20] Points for the BODE Index were assigned as described by Celli *et al*.[27]

CV hospitalisation and mortality

CV hospitalisation and mortality data were extracted from the linked hospital admission data and death certificates. Non-fatal CV episodes were extracted from both primary and secondary International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10) coding positions. Causes of death were adjudicated by CV and pulmonary physicians. We defined

the primary outcome as first reported occurrence (since study enrolment) of fatal or non-fatal hospitalised CVD, where CVD was defined as disease of the arteries, stroke or heart failure (see online supplemental table 1) based on classifications used by the Emerging Risk Factors Collaboration.[28] Time to primary outcome was calculated from the difference between the baseline visit date (starting December 2011) and either the date of death or first hospitalised CV attendance up to November 2017, when follow-up discontinued. Secondary outcomes of interest were all-cause and cause-specific mortality (defined as CV, pulmonary, cancer or other).

Risk factors of interest

Conventional CVD risk factors included age, sex, self-reported smoking status (current/ex-smoker), high-density lipoprotein (HDL) cholesterol, total cholesterol, systolic blood pressure (SBP), diabetes (yes/no) and treatment for high blood pressure (yes/no). We also assessed the addition of the following risk factors: BMI, aPWV and CIMT, fasting glucose, CRP and fibrinogen, COPD severity (ie, GOLD stage and BODE Index) and measures of physical performance (ie, 6MWT and 4MGS).

Statistical analysis

HRs with 95% CIs were estimated using Cox regression models stratified by study centre. Age and sex were added to all models. To quantify the independent association of CIMT, we further included SBP. For aPWV, we also included mean arterial pressure and resting heart rate. For AIx, we additionally included resting heart rate and height. Proportional hazards were assessed by Schoenfeld's global tests. We assessed the relationships of the new markers and outcomes and consequently log-transformed the following risk factors: CRP, fibrinogen and glucose. HRs for log-transformed risk factors represented a twofold increase in the risk factor, whereas others were presented as a change in unit. We evaluated the predictive value of new markers added to the conventional CVD risk factors using measures of discrimination (ie, Harrell's C-statistic)[29 30] and calibration (ie, Gronnesby and Borgan test and Brier score). The Gronnesby and Borgan test is an overall calibration test for Cox models based on grouping individuals by their estimated risk score and compares observed and model-based expected events within each group (a p value of $>\alpha$ suggests no difference). Brier scores range from 0 to 1 (0 is perfect accuracy and 1 is perfect inaccuracy) and allow comparison of performance of a model with a reference model. The C-statistic is a measure for validating the discriminative ability of a model. Values range from 0.5 to 1.0 (1.0 is a perfect prediction and 0.5 is a random guess). A higher score indicates better discriminative ability of the model. To optimise efficiency and to avoid optimism from internal validation in small samples, we used 10-fold cross validation with 200 replications[31] (see online supplemental text 1 and online supplemental figures 1–5 for further statistical analyses details).

Table 1 Baseline characteristics (N=714)

Characteristics	Summary measures
Conventional CVD risk factors	
Age (years)	67 (62–73)
Male	434 (61)
Current smoker	218 (31)
HDL (mmol/L)	1.4 (1.2–1.7)
Cholesterol (mmol/L)	5.0 (4.3–5.8)
SBP (mm Hg)	142 (131–154)
Diabetes mellitus	82 (12)
Drugs to treat hypertension	245 (34)
CV measures	
aPWV (m/s)	9.8 (8.4–11.8)
CIMT (mm)	0.81 (0.71–0.96)
Alternative measures	
CRP (mg/L)	1.21 (0.47–2.01)
Fibrinogen (g/dL)	1.22 (1.06–1.36)
Glucose (mmol/L)	1.59 (1.46–4.59)
BMI (kg/m^2)	27 (23–31)
GOLD (stage)	2 (2–3)
4MGS (m/s)	0.95 (0.77–1.14)
6MWT distance (m)	366 (255–440)
BODE (point)	3 (1–5)

Values are given as median and IQR, or number of cases (%).
aPWV, aortic pulse wave velocity; BMI, body mass index; BODE, Body mass index, airflow Obstruction, Dyspnoea and Exercise capacity; CIMT, carotid intima–media thickness; CRP, C reactive protein; CV, cardiovascular; CVD, cardiovascular disease; GOLD, Global Initiative for Chronic Obstructive Lung Disease; HDL, high-density lipoprotein; 4MGS, 4 m gait speed; 6MWT, 6 min walk test; SBP, systolic blood pressure.

Observational data are reported according to the Strengthening the Reporting of Observational Studies in Epidemiology statement.[32] All tests were two-sided and statistical significance was defined by 95% CI for HRs not traversing 1 or p<0.05. Our analyses were performed using STATA V.13 and R (R Foundation).

RESULTS

Of the 729 individuals included in the study, 714 (98%) could be linked with hospital admission and survival records, and were included in the analysis (online supplemental figure 6). The median age was 67 (IQR 62–73) years, and 434 (61%) individuals were male (table 1). A third (n=218) of the cohort smoked; 12% (n=82) had self-reported diabetes; 34% (n=245) were taking antihypertensive medications; and 31% (n=224) were taking cholesterol-lowering medications at baseline. The median FEV_1 was 1.3 L (0.9–1.7 L) (mean±SD=1.34±0.53). In total, 192 individuals (27%) had a first event of CV hospitalisation (peripheral arterial disease (n=9), diseases of

Risk factor	Median (IQR) or n (%)	HR (95% CI)[a]	HR (95% CI)[b]	C–statistic
All conventional CVD risk factors				0.689 [0.688 to 0.691]
Age – per 10 year increase	67 (62–73)	1.58 (1.30 to 1.92)	1.59 (1.29 to 1.99)	0.619 [0.618 to 0.621]
Sex – male	434 (61)	1.28 (0.94 to 1.74)	1.16 (0.84 to 1.60)	0.585 [0.581 to 0.588]
Smoking – current	218 (31)	0.95 (0.68 to 1.31)	0.92 (0.66 to 1.29)	0.515 [0.512 to 0.517]
HDL – per 1 mmol/L increase	1.4 (1.2–1.7)	0.73 (0.52 to 1.03)	0.86 (0.60 to 1.23)	0.571 [0.569 to 0.573]
Cholesterol – per 1 mmol/L increase	5.0 (4.3–5.8)	0.80 (0.70 to 0.92)	0.89 (0.76 to 1.03)	0.613 [0.611 to 0.614]
SBP – per 10 mmHg increase	142 (131–154)	0.91 (0.84 to 0.99)	0.90 (0.82 to 0.98)	0.532 [0.530 to 0.535]
Diabetes – yes	82 (12)	1.50 (1.01 to 2.22)	1.15 (0.76 to 1.75)	0.538 [0.534 to 0.539]
Hypertension medication – yes	245 (34)	1.79 (1.34 to 2.38)	1.76 (1.31 to 2.36)	0.620 [0.616 to 0.623]

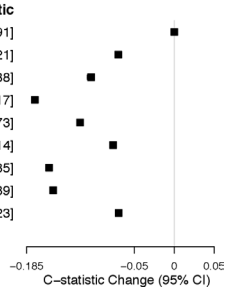

Figure 1 Conventional CVD risk factors at baseline, their HRs and discriminative ability for fatal or non-fatal hospitalised CVD. Values are given as median and IQR, or number of cases (%). Baseline data of 714 patients are included. All models are stratified by recruitment site. There were <5% missing values for descriptive variables such as body mass index and smoking status. Missing values were addressed using multiple imputations using chained equations. [a]Model includes age and sex. [b]Model includes conventional CVD risk factors: age, sex, smoking, HDL, total cholesterol, SBP, diabetes and hypertension medication. CVD, cardiovascular disease; HDL, high-density lipoprotein; SBP, systolic blood pressure.

arteries, arterioles and capillaries (n=7), angina (n=21), unstable angina (n=3), coronary heart disease not otherwise specified (n=63), acute myocardial infarction (MI) and certain current complications following acute MI (n=11), cerebral infarction (n=11), stroke, not specified as haemorrhage or infarction (n=3), other stroke (n=18), heart failure (n=32) and abdominal aortic aneurysm (n=8); n=116 (60%) were in ICD-10 secondary coding position) during median follow-up for 4.6 years, and 6 individuals had CV death without any preceding CV episode. CV hospitalisation accounted for the majority (97%) of events analysed. The CV incidence rate was 6.7 (95% CI 5.8 to 7.7) per 100 person-years (see online supplemental tables 1 and 2) for categorisation of different admission codes for CV hospitalisation.

Conventional CVD risk factors

Of the conventional CVD risk factors, age and treatment for high blood pressure had significant positive associations with the study's outcome, whereas SBP had a significant negative association and other risk factors (ie, sex, smoking status, cholesterol, HDL cholesterol and diabetes) were not significantly associated with CV hospitalisation. Use of hypertension drug treatment followed by age and total cholesterol contributed most to the discriminative ability of the model. The overall discriminative ability of the CV risk model had a C-statistic of 0.689 (95% CI 0.688 to 0.691, figure 1 and online supplemental table 3).

Surrogate CV risk markers

Except for AIx, neither aPWV nor CIMT was significantly associated with CV hospitalisation after including conventional CVD risk factors (figure 2 and online supplemental table 4). Moreover, none of the CV risk markers significantly changed the discriminative ability of the CV risk model.

Physical performance measures, COPD severity and inflammatory markers

Multivariable analysis identified that poor physical performance (ie, reduced 6MWT distance and slower 4MGS) was significantly associated with increased CV hospitalisation, independently of conventional CVD risk factors. With the exception of glucose and BMI, severity of COPD defined by higher BODE Index and GOLD stage, as well

Risk factor	Median (IQR) or n (%)	HR (95% CI)[a]	HR (95% CI)[b]	C–statistic
All conventional CVD risk factors				0.689 [0.688 to 0.691]
+ PWV – per 1 m/sec increase	9.8 (8.4–11.8)	1.01 (0.95 to 1.07)	0.99 (0.93 to 1.06)	0.691 [0.689 to 0.692]
+ CIMT – per 1 mm increase	0.81 (0.71–0.96)	1.09 (0.49 to 2.45)	1.08 (0.48 to 2.43)	0.691 [0.690 to 0.693]
+ AIx – per 5% increase	28 (20–34)	0.85 (0.77 to 0.93)	0.90 (0.82 to 0.99)	0.688 [0.686 to 0.689]

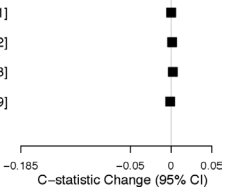

Figure 2 Aortic stiffness at baseline, their HRs and discriminative ability for fatal or non-fatal hospitalised CVD. Values are given as median and IQR, or number of cases (%). Baseline data of 714 patients are included. All models are stratified by recruitment site. Gronnesby and Borgan goodness of fit ($\chi^2(3)$, $p>\chi^2$): CV risk model (2.07, 0.559), aPWV (1.64, 0.652), CIMT (2.32, 0.509), and AIx (3.08, 0.380). Estimates based on quartiles of risk. Brier score: CV risk model 0.129 (95% CI 0.111 to 0.146), aPWV 0.126 (95% CI 0.108 to 0.145), CIMT 0.128 (95% CI 0.110 to 0.147) and AIx 0.126 (95% CI 0.109 to 0.144). Lower score indicates better accuracy of estimates. [a]Model includes age and sex. [b]Model includes conventional CVD risk factors: age, sex, smoking, high-density lipoprotein, total cholesterol, SBP, diabetes and hypertension medication. CIMT further included SBP. Carotid–femoral aPWV further included mean arterial pressure and resting heart rate. AIx further included resting heart rate and height. There were about 10% missing values for variables CIMT (n=66) and aPWV (n=60). Missing values were addressed using multiple imputations using chained equations. AIx, Augmentation Index; aPWV, aortic pulse wave velocity; CIMT, carotid intima–media thickness; CV, cardiovascular; CVD, cardiovascular disease; PWV, pulse wave velocity; SBP, systolic blood pressure.

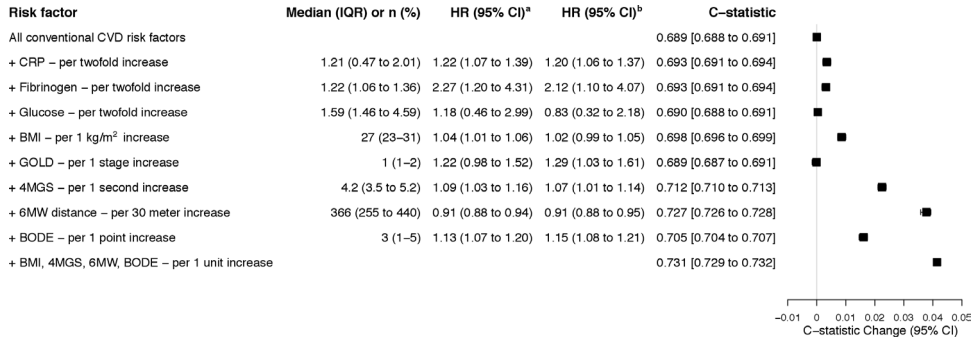

Figure 3 Alternative measures at baseline, their HRs and discriminative ability for fatal or non-fatal hospitalised CVD. Values are given as median and IQR, or number of cases (%). Baseline data of 714 patients are included. All models are stratified by recruitment site. Gronnesby and Borgan goodness of fit ($\chi^2(3)$, $p>\chi^2$): CV risk model (2.07, 0.559); CRP (0.32, 0.956); fibrinogen (1.48, 0.687); glucose (0.42, 0.936); BMI (1.56, 0.668); GOLD (5.63, 0.131); 4MGS (4.70, 0.195); 6MWT (2.94, 0.401); BODE (6.46, 0.091); BMI, 4MGS, 6MWT, bode (4.12, 0.249). Estimates based on quartiles of risk. Brier score: CV risk model 0.129 (95% CI 0.111 to 0.146); CRP 0.125 (95% CI 0.107 to 0.142); fibrinogen 0.128 (95% CI 0.111 to 0.146); glucose 0.128 (95% CI 0.111 to 0.146); BMI 0.128 (95% CI 0.111 to 0.146); GOLD 0.128 (95% CI 0.110 to 0.146); 4MGS 0.127 (95% CI 0.110 to 0.144); 6MWT 0.123 (95% CI 0.105 to 0.140); BODE 0.124 (95% CI 0.106 to 0.142); BMI, 4MGS, 6MWT, BODE 0.122 (95% CI 0.104 to 0.140). Lower score indicates better accuracy of estimates. [a]Model includes age and sex. [b]Model includes conventional CVD risk factors: age, sex, smoking, high-density lipoprotein, total cholesterol, systolic blood pressure, diabetes and hypertension medication. There were <5% missing values for biochemical markers, including fibrinogen and cholesterol. Missing values were addressed using multiple imputations using chained equations. 4MGS, 4 m gait speed; 6MWT, 6 min walk test; BMI, body mass index; BODE, Body mass index, airflow Obstruction, Dyspnoea, and Exercise capacity; CRP, C reactive protein; CV, cardiovascular; CVD, cardiovascular disease; GOLD, Global Initiative for Chronic Obstructive Lung Disease.

as inflammatory markers (ie, CRP and fibrinogen), all had significant positive associations with CV hospitalisations independently of conventional CVD risk factors.

Predictive modelling indicated significant improvement in risk discrimination when adding BMI (C=0.698, 95% CI 0.696 to 0.699), BODE (C=0.705, 95% CI 0.704 to 0.707), 4MGS (C=0.712, 95% CI 0.710 to 0.713) or 6MWT (C=0.727, 95% CI 0.726 to 0.728) to the CV risk model, but not GOLD stage, inflammatory markers or glucose (figure 3 and online supplemental table 5). Calibration tests indicate good model fit (figures 2 and 3). Adding BMI, 4MGS, 6MWT and BODE collectively to the CV risk model resulted in a C-statistic of 0.731 (95% CI 0.729 to 0.732), indicating 6MWT primarily accounted for improved discriminative ability of the model. The model including 6MWT had a better Brier score relative to the CV risk model (0.123 vs 0.129, respectively).

All-cause and cause-specific mortality

There were 144 deaths in total (nearly 20% of the cohort) over a median follow-up period of 4.6 years. The majority of deaths were in men (n=96, 67%), and pulmonary disease was the leading cause in both sexes (table 2). Pulmonary disease accounted for 65% of deaths in women and 50% in men, followed by cancer (19% in women, 27% in men), CV (6% and 16%) and other (10% and 7% in women and men, respectively).

DISCUSSION

This is the first study assessing the utility of conventional CVD risk factors for CV risk prediction and the value of additional markers of risk within a COPD cohort. Novel findings include (1) poor physical performance improved the discriminative power when added to the CV risk model; (2) BODE Index, GOLD stage, 4MGS and systemic inflammatory markers were positively associated with CV hospitalisations independently of conventional CVD risk factors, although they collectively improved the model's discriminative ability marginally; and (3) of the conventional CVD risk factors, age, SBP and use of antihypertensives were positively associated with study outcome. However, age, cholesterol and use of antihypertensives contributed most to the model's prognostic power. SBP had a significant negative association with CV hospitalisations but did not add to the model's predictive ability. Furthermore, aPWV and CIMT, despite providing in vivo mechanistic information about the arterial system, had no significant association with CV hospitalisations, whereas AIx did. Therefore, these data suggest that in COPD, physical performance (assessed by 6MWT) contributes to CV risk estimation defined predominantly

Table 2 Mortality in the Evaluation of the Role of Inflammation in Chronic Airways disease cohort

Cause-specific mortality	Female, n (%)	Male, n (%)	Total, N (%)
Pulmonary	31 (65)	48 (50)	79 (55)
Cardiovascular	3 (6)	15 (16)	18 (13)
Cancer	9 (19)	26 (27)	35 (24)
Other	5 (10)	7 (7)	12 (8)
All-cause	48 (100)	96 (100)	144 (100)

Deaths recorded over a median follow-up of 4.6 years.

by non-fatal CV hospitalisations. Finally, CVD contributed to only a small number of deaths at a median follow-up of 4.6 years. Pulmonary disease, followed by cancer, was the major cause of death in both men and women with COPD.

We observed a C-statistic of 0.689 based on the conventional CV risk model, which increased to a maximum of 0.731 when adding additional markers; this increment was primarily due to 6MWT. These C-statistic values indicate a moderate predictive ability of the models for the study's outcome. For perspective, a C-statistic of 0.53 was observed in a Framingham model in the very elderly (aged 85-plus years; the median age of our cohort was 67 years) without prior CVD, indicating it does not predict CV mortality in this group.[6] However, in primary care individuals without CVD in the Framingham study, a C-statistic of 0.76 for an outcome of general CVD (ie, coronary heart disease, stroke, peripheral artery disease or heart failure) demonstrated good discrimination.[10] Since our cohort included individuals with CVD at baseline, and different CVD risk factors and CV outcomes are evaluated in various studies, no direct comparison of study results can be made. That aPWV was not predictive in our cohort contrasts with findings reported by Ben-Shlomo *et al*. However, from the 17 included cohorts in their study, none were COPD cohorts; the mean age of the cohorts was lower; and the proportion of individuals taking drugs to treat hypertension was higher.[14]

Overall, our study emphasises the importance of physical function as a predictor of CV risk. Tests such as 6MWT or 4MGS are proxy measures of overall mobility and physical functioning.[33] Exercise capacity and CV fitness are known to be associated with fatal and non-fatal CVD,[34] while exercise-based cardiac rehabilitation reduces risk of CV events.[35] The 6MWT distance is prognostic in patients with stable coronary heart disease[12] and in those with moderate-to-severe heart failure.[36]

In our cohort, poor physical function improved discriminative ability of the CV risk model beyond conventional CVD factors. This has implications for clinical practice in CV risk assessment for individuals with COPD, suggesting it may be helpful to incorporate physical performance into clinical assessment. Especially those aged under 65 years may benefit most from active CVD assessment, according to Morgan *et al*.[37] However, given that 6MWT can be logistically challenging to set up and time-consuming,[38] the faster and simpler 4MGS that also significantly improved the C-statistic could be used as a simpler alternative. In elderly with CVD, 4MGS is comparable to 6MWT in predicting all-cause mortality.[39]

The BODE Index also significantly improved the C-statistic of the CV risk model. However, this was primarily due to the 6MWT component. In fact, although GOLD stage had a significant positive association with the study outcome, this did not improve the prognostic power of the model. Therefore, despite the association between airflow limitation and CV risk in general population studies,[17 40] in patients with COPD, physical performance assessment rather than another component of BODE (ie, spirometry) adds value to CV risk prediction.

Although we did not find an association between inflammatory markers and surrogate markers of CV risk in the baseline cross-sectional component of the ERICA study,[41] both CRP and fibrinogen were associated with CV hospitalisations captured over nearly 5 years of follow-up. That the associations remained significant after including conventional CVD risk factors indicates potential value for identifying high-risk individuals within a COPD population. The inverse relationship of SBP was an unexpected finding. One hypothesis is that SBP has a J-shaped curve for CV events and mortality.[42] Therefore, in this cohort, lower SBP might be a marker of sickness and frailty, hence its association with CV hospitalisations.

A third of the cohort had a CV-related hospitalisation during follow-up, and the majority had pre-existing CV comorbidity at baseline. The high numbers of CV hospitalisations give perspective of what this comorbidity incurs for patients and the huge healthcare costs involved. In contrast to the sizeable number of CV hospitalisations was the small number of CV deaths. Gayle *et al* previously reported that CV-related mortality in patients with chronic lung disease had already started to decline in England.[43] This may reflect better CV risk management reducing CV mortality. Importantly though, such risk management does not seem to impact CV morbidity and is an area that requires future research to determine the optimum approach to impact CV morbidity in individuals with COPD.

Nearly 20% of the cohort died during follow-up. This is comparable to the TOwards a Revolution in COPD Health (TORCH) study where approximately 15% of the cohort died over 3 years of follow-up.[2] Pulmonary disease, followed by cancer, accounted for proportionally more deaths in our cohort compared with TORCH, whereas CV-specific mortality was less (10%–15% vs 27% in TORCH). Reasons for these findings are not entirely understood, but the sizeable proportion of our cohort already on medicines for dyslipidaemia and blood pressure control may be an important factor.

Our study has limitations. The conventional CVD risk factors are usually used to predict CV risk defined by development of CVD. However, the majority of our participants already had CVD and were on CV medications, which may be a confounding factor impacting the discriminative ability of CVD risk factors. Moreover, in our study, CV risk was defined differently (as CV hospitalisation with CV mortality). Hospitalised CV episodes were coded based on ICD-10 classifications[28] extracted from both primary and secondary positions. Notably, most CV hospitalisations were recorded in secondary positions, indicating that the primary admission might be related to something else. Due to the few CV events recorded in the primary position, we were unable to conduct a sensitivity analysis including CV events in the primary position only. The study period covered the time from study enrolment until the end of study or death. Some

individuals, however, may have been admitted to hospital for CV events before study enrolment. We were unable to obtain HES data outside this period. Competing risks may have occurred, for example, individuals who died of other causes may not have experienced a CV event during the study period for this reason. However, our study did not have sufficient statistical power to assess this. It is possible our models predict non-CV hospitalisation due to, for example, potential cross-contamination of COPD and CV hospitalisation as a result of misclassification of morbidity and mortality that often occurs when data are obtained from routine sources.[44] Deprivation scores may be another important determinant of CV risk in individuals with COPD that is worth evaluating in future research,[45] although the relatively small cohort size of our study meant we did not include this in the analysis.

Furthermore, follow-up time for the study was a maximum of 5 years, whereas risk scores such as Framingham Risk Score and QRISK calculate a 10-year risk. Hence, the prognostic value of variables may alter with a different time horizon and depends on the extent of time trends in the new biomarkers. For example, a too short time period may result in an insufficient number of events, while over a longer time period, for example, 20 years, the predictive ability would diminish because ageing is a strong predictor. We did not have access to an independent validation cohort but used cross-validation techniques instead. Generalisability of our results is limited to those with moderate COPD in the UK with NHS hospitalisations.

CONCLUSION

In a UK COPD cohort, poor physical performance assessed by 6MWT or 4MGS and inflammatory biomarkers are associated with subsequent CV-related hospitalisations, independently of conventional CVD risk factors. Importantly, poor physical performance (defined primarily by 6MWT) also significantly improved the predictive discrimination of the CV risk model. These data suggest an assessment of physical performance may enhance CV risk evaluation in individuals with COPD.

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Disclaimer The views and opinions expressed are those of the authors and do not necessarily reflect those of the University of Cambridge, the NHS, the National Institute for Health Research, the Department of Health and Social Care or other parent institutions of the authors. The corresponding author and IBW had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Competing interests GSK, a consortium partner, funded JMF's PhD. HM, RT-S and DM were employees of GSK at the time this work was completed and own GSK shares and stock options. JC is employed by Cambridge University Hospitals NHS Foundation Trust and is obligated to spend 50% of his time on GSK clinical trial activity, representing a significant relationship; however, he receives no other benefits or compensation from GSK. MIP received grants from GSK outside the submitted work. IBW received grants from GSK during the conduct of the study and outside the submitted work.

Patient consent for publication Not required.

Ethics approval Informed patient consent was obtained in writing from all study participants and permits the publishing of all data included in this article. The investigation conforms with the principles outlined in the Declaration of Helsinki. Ethical approval was granted by the National Research Ethics Service Committee East of England, Cambridge South (11/EE/0357).

Data availability statement Data are available upon reasonable request. Data may be obtained from a third party and are not publicly available. The dataset underlying these findings, with deidentified participant data (including the data dictionary), are available to interested and qualified researchers upon request and can be obtained from the Cambridge Clinical Trials Unit. Access to hospital episode

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Supplementary materials for “Cardiovascular risk prediction using physical performance measures in COPD: results from a multi-centre observational study.”

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Supplementary text

Text 1 Supplementary methods

There were missing values. Data were assessed for the level and type of missing data, and completion patterns (Figures 1-2). There were about 10% missing values for variables CIMT (n = 66) and PWV (n = 60), with <5% missing values for other variables (Figures 3-5). Missing values were addressed using multiple imputations using chained equations (MICE). The time-to-event outcome was included using the non-parametric Nelson-Aalen estimator. Predictive mean matching was used for continuous variables, ordered logistic regression (as continuous) for ordinal variables, multinomial logistic regression for categorical variables, and logistic regression for binary variables. Derived variables such as the BODE Index (a composite score of BMI, forced expiratory volume in one second (FEV_1), Medical Research Council dyspnoea score, and 6MWT distance) and GOLD stage were estimated post MICE using passive imputation.

Data were cleaned for episode status, and inpatient (i.e. hospitalised) CV episodes were identified based on classifications used by the Emerging Risk Factors Collaboration.[1] Cardiovascular events were extracted from both primary and secondary positions of ICD-10. Priority was given to CV events reported in the primary position (n = 70). Following this, we selected CV events in the secondary position (n = 116), which had no recording of a CV event in the primary position. Only episodes during the study follow-up were evaluated.

[1] The Emerging Risk Factors Collaboration: analysis of individual data on lipid, inflammatory and other markers in over 1.1 million participants in 104 prospective studies of cardiovascular diseases. *Eur J Epidemiol* **22,** 839–869 (2007). https://doi.org/10.1007/s10654-007-9165-7

Supplementary tables

Table 1 Definitions of diagnoses by ICD-10 coding.

End point	ICD-10 codes
All cardiovascular disease	**F01, G46.3-G46.7, G458, G459 I11.0, I13.0, I13.2, I20.0-I20.1, I20.8-I25, I50, I60, I61, I.62, I63, I64, I65-I69, I70.2, I71.3-I71.9, I72, I73.9-I79 + cardiac death**
Diseases of the arteries	**I70.2, I72, I73.9-I79**
Peripheral arterial disease	I70.2, I73.9
Diseases of arteries, arterioles and capillaries	I72, I74-I79
Coronary heart disease	**I20.0-I20.1, I20.8-I25**
Angina	I20.1, I20.8-I20.9
Unstable angina	I20.0, I24
Coronary heart disease not otherwise specified	I25
Acute myocardial infarction (MI), and certain current complications following acute MI	I21, I23
Subsequent myocardial infarction	I22
All stroke	**I60, I61, I.62, I63, I64, I65-I69, F01, G46.3-G46.7, G458, G459**
Subarachnoid haemorrhage	I60
Intra-cerebral haemorrhage	I61
Cerebral infarction	I63
Stroke, not specified as haemorrhage or infarction	I64
Stroke syndromes	G46.3-G46.7
Transient ischemic attack	G458, G459
Other stroke	I62, I65-I69, F01
Heart failure	**I11.0, I13.0, I13.2, I50**
Heart failure	I50
Hypertensive heart disease with (congestive) heart failure	I11.0
Hypertensive heart and renal disease with (congestive) heart failure	I13.0
Hypertensive heart and renal disease with both (congestive) heart failure and renal disease	I13.2
Cardiac death	**Adjudicated**
Other vascular deaths	**I71.3-I71.9**
Abdominal aortic aneurysm	I71.3-I71.9

Table 2 Fatal or non-fatal hospitalised cardiovascular disease by ICD-10 coding position.

	All cardiovascular disease			AECOPD	
	Primary ICD-10 position	**Secondary ICD-10 position**	**Cardiac death**	**Primary ICD-10 position**	**Secondary ICD-10 position**
1	I714			J441	
2	I209			J441	
3	I501				
4	I771			J440	
5	I251				
6	I251				
7	I219				J440
8	I251				
9	I745				
10	I259				
11	I251			J441	
12	I251				
13	I500			J440	
14	I743			J441	
15	I64X			J440	
16	I714				
17	I219			J440	
18	I211				
19	I64X				
20	I739				
21	I739				
22	I639				
23	I251			J441	
24	I652				
25	I251			J440	
26	I251				
27	I632				
28	I251			J440	
29	I660			J440	
30	I500			J441	
31	I771				
32	I251			J441	
33	I638			J441	
34	I702			J440	
35	I200			J441	
36	I652				
37	I501			J441	
38	I214				
39	I64X			J440	
40	I509				
41	I739				
42	I739				
43	I639				J440
44	I743				
45	I251				
46	I251			J440	
47	I219				
48	I638				
49	I251			J440	
50	I251			J440	
51	I639				J440

52	I500				
53	I251				
54	I251			J441	
55	I639				
56	I652				J440
57	I219				
58	I635				
59	I214			J440	
60	I251				
61	I739				J440
62	I639				
63	I251			J440	
64	I200				J440
65	I214				J440
66	I251				
67	I634				J440
68	I209				J440
69	I714				
70	I509				
71		I209		J440	
72		I501			
73		I713			J440
74		I714			
75		I252			J440
76		I259		J440	
77		I252		J440	
78		I500		J441	
79		I694			
80		I209			
81		I209			
82		I259		J441	
83		I509		J440	
84		I500			J440
85		I509			J440
86		I200			
87		I219		J440	
88		I714			J440
89		I780			J440
90		I219		J440	
91		I252		J440	
92		I714		J441	
93		I209			J440
94		I251		J440	
95		I259			J440
96		I501		J440	
97		I252			
98		I252			
99		I500			J440
100		I252			J440
101		I252			
102		I652			
103		I500		J440	
104		I259		J441	
105		I251			
106		I501		J440	
107		I252			
108		I255			J440
109		I259			J440

110		I500		J440	
111		I252			
112		I252		J440	
113		I259			
114		I678		J441	
115		I501			J440
116		I678		J440	
117		I501			J440
118		I678		J440	
119		I259			
120		I209			
121		I209		J441	
122		I500		J441	
123		I259			J440
124		I259			J440
125		I259			J440
126		I209		J440	
127		I252			J440
128		I509		J440	
129		I209			
130		I259			
131		I259			
132		I259		J440	
133		I209			
134		I679			
135		I678		J440	
136		I500		J440	
137		I501			
138		I500		J441	
139		I209			
140		I652		J440	
141		I209			
142		I678			
143		I209			
144		I209		J441	
145		I501		J441	
146		I209		J440	
147		I209		J440	
148		I739			
149		I509			
150		I678		J441	
151		I252		J440	
152		I252			
153		I501		J440	
154		I678			
155		I251		J440	
156		I252			J440
157		I500		J440	
158		I252		J440	
159		I252		J440	
160		I634			
161		I679			
162		I252		J440	
163		I252			
164		I500			J440
165		I209		J441	
166		I739			J440
167		I739		J440	

168		I259			
169		I509			J440
170		I252			
171		I209			J440
172		I798		J440	
173		I500			
174		I209			
175		I501		J440	
176		I219		J441	
177		I209			
178		I252		J440	
179		I252			
180		I671		J441	
181		I259			
182		I259		J440	
183		I671			
184		I259			J440
185		I251			J440
186		I714			J440
187			Cardiac		
188			Cardiac		
189			Cardiac		
190			Cardiac		
191			Cardiac		
192			Cardiac		
Total recorded	70	116	6	74	35

Twenty-five individuals with a CV event recorded in the primary position also had an acute exacerbation of COPD (AECOPD) recorded in the primary position during the study period. In addition, 49 individuals with a CV event recorded in the secondary position also had an AECOPD recorded in the primary position during the study period.

Table 3 Conventional cardiovascular disease risk factors at baseline, their hazard ratios for cardiovascular disease.

	Median (IQR) or No. (%)	HR (95% CI)[a]	P value	HR (95% CI)[b]	P value
Conventional CVD risk factors					
Age – per 10 year increase	67 (62-73)	1.58 (1.30 to 1.92)	< 0.001	1.59 (1.29 to 1.99)	< 0.001
Sex – males	434 (61)	1.28 (0.94 to 1.74)	0.113	1.16 (0.84 to 1.60)	0.375
Smoking – current	218 (31)	0.95 (0.68 to 1.31)	0.744	0.92 (0.66 to 1.29)	0.632
HDL – per 1 mmol/L increase	1.4 (1.2-1.7)	0.73 (0.52 to 1.03)	0.074	0.86 (0.60 to 1.23)	0.402
Total cholesterol – per 1 mmol/L increase	5.0 (4.3-5.8)	0.80 (0.70 to 0.92)	0.002	0.89 (0.76 to 1.03)	0.118
SBP – per 10 mmHg increase	142 (131-154)	0.91 (0.84 to 0.99)	0.023	0.90 (0.82 to 0.98)	0.016
Diabetes – yes	82 (12)	1.50 (1.01 to 2.22)	0.044	1.15 (0.76 to 1.75)	0.511
Hypertension treatment – yes	245 (34)	1.79 (1.34 to 2.38)	< 0.001	1.76 (1.31 to 2.36)	< 0.001

Values are given as the median and interquartile range (IQR), or No. of cases (%). Baseline data of 714 patients are included. All models are stratified by recruitment site.
[a]Model includes age and sex.
[b]Model includes conventional cardiovascular disease risk factors: age, sex, smoking, high-density lipoprotein, total cholesterol, systolic blood pressure, diabetes, hypertension drug treatment.
CI = confidence interval. HDL = high-density lipoprotein. SBP = systolic blood pressure. CV = cardiovascular.

Table 4 Arterial stiffness at baseline, their hazard ratios for cardiovascular disease.

	Median (IQR) or No. (%)	HR (95% CI)[a]	P value	HR (95% CI)[b]	P value
Measures of arterial stiffness					
PWV – per 1 m/sec increase	9.8 (8.4-11.8)	1.01 (0.95 to 1.07)	0.796	0.99 (0.93 to 1.06)	0.749
CIMT – per 1 mm increase	0.81 (0.71-0.96)	1.09 (0.49 to 2.45)	0.827	1.08 (0.48 to 2.43)	0.861
AIx – per 5% increase	28 (20-34)	0.85 (0.77 to 0.93)	< 0.001	0.90 (0.82 to 0.99)	0.027

Values are given as the median and interquartile range (IQR), or No. of cases (%). Baseline data of 714 patients are included. All models are stratified by recruitment site.
[a]Model includes age and sex.
[b]Model includes conventional cardiovascular disease risk factors: age, sex, smoking, high-density lipoprotein, total cholesterol, systolic blood pressure, diabetes, hypertension drug treatment.
Carotid intima-media thickness further included systolic blood pressure. Carotid-femoral aortic pulse wave velocity further included mean arterial pressure and resting heart rate. AIx further included resting heart rate and height.
CI = confidence interval. PWV = pulse wave velocity. CIMT = carotid intima-media thickness. AIx = augmentation index.

Table 5 Alternative measures at baseline, their hazard ratios for cardiovascular disease.

	Median (IQR) or No. (%)	HR (95% CI)[a]	P value	HR (95% CI)[b]	P value
Other risk factors					
CRP – per twofold increase	1.21 (0.47 to 2.01)	1.22 (1.07 to 1.39)	0.002	1.20 (1.06 to 1.37)	0.005
Fibrinogen – per twofold increase	1.22 (1.06 to 1.36)	2.27 (1.20 to 4.31)	0.012	2.12 (1.10 to 4.07)	0.024
Glucose – per twofold increase	1.59 (1.50 to 1.69)	1.18 (0.46 to 2.99)	0.730	0.83 (0.32 to 2.18)	0.709
BMI – per 1 kg/m^2 increase	27 (23-31)	1.04 (1.01 to 1.06)	0.002	1.02 (0.99 to 1.05)	0.089
GOLD – per 1 stage increase	1 (1-2)	1.22 (0.98 to 1.52)	0.071	1.29 (1.03 to 1.61)	0.026
4MGST – per 1 second increase	4.2 (3.5 to 5.2)	1.09 (1.03 to 1.16)	0.002	1.07 (1.01 to 1.14)	0.020
6MWT distance – per 30 metre increase	366 (255 to 440)	0.91 (0.88 to 0.94)	< 0.001	0.91 (0.88 to 0.95)	< 0.001
BODE – per 1 point increase	3 (1-5)	1.13 (1.07 to 1.20)	< 0.001	1.15 (1.08 to 1.21)	< 0.001

Values are given as the median and interquartile range (IQR), or No. of cases (%). Baseline data of 714 patients are included. All models are stratified by recruitment site.
[a]Model includes age and sex.
[b]Model includes conventional cardiovascular disease risk factors: age, sex, smoking, high-density lipoprotein, total cholesterol, systolic blood pressure, diabetes, hypertension drug treatment.
CI = confidence interval. CRP = C-reactive protein. BMI = body mass index. GOLD = global initiative for chronic obstructive lung disease. 4MGS = four-metre gait speed. 6MWT = six-minute walk test. BODE = body mass index, obstruction, dyspnoea, exercise.

Supplementary figures

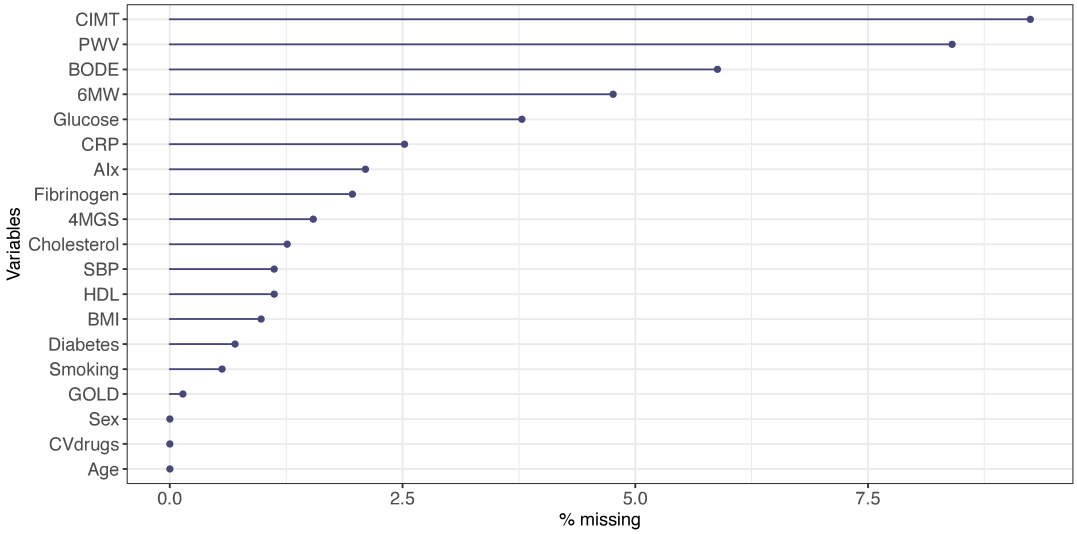

Figure 1 Percentage of missing values.
CIMT = carotid intima-media thickness. PWV = pulse wave velocity. BODE = body mass index, obstruction (i.e. forced expiratory volume in one second), dyspnoea score, exercise (i.e. six-minute walk test distance). 6MWT = six-minute walk test. CRP = C-reactive protein. AIx = augmentation index. 4MGS = four-metre gait speed. SBP = systolic blood pressure. HDL = high-density lipoprotein. BMI = body mass index. GOLD = global initiative for obstructive lung disease. CV = cardiovascular.

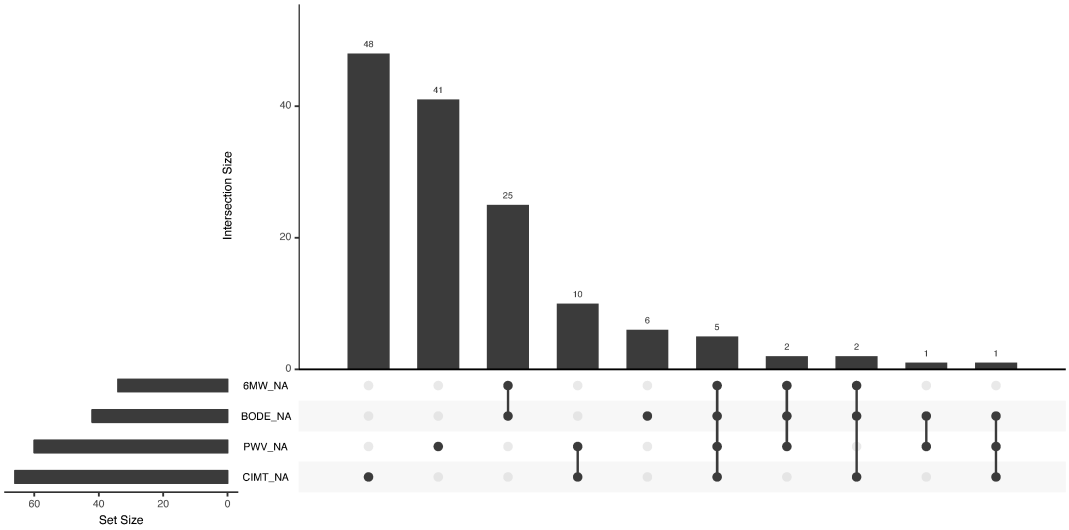

Figure 2 Percentage and pattern of missing values in key baseline characteristics.
6MWT, six-minute walk test. BODE = body mass index, obstruction (i.e. forced expiratory volume in one second), dyspnoea score, exercise (i.e. six-minute walk test distance). PWV, pulse wave velocity. CIMT, carotid-intima media thickness.

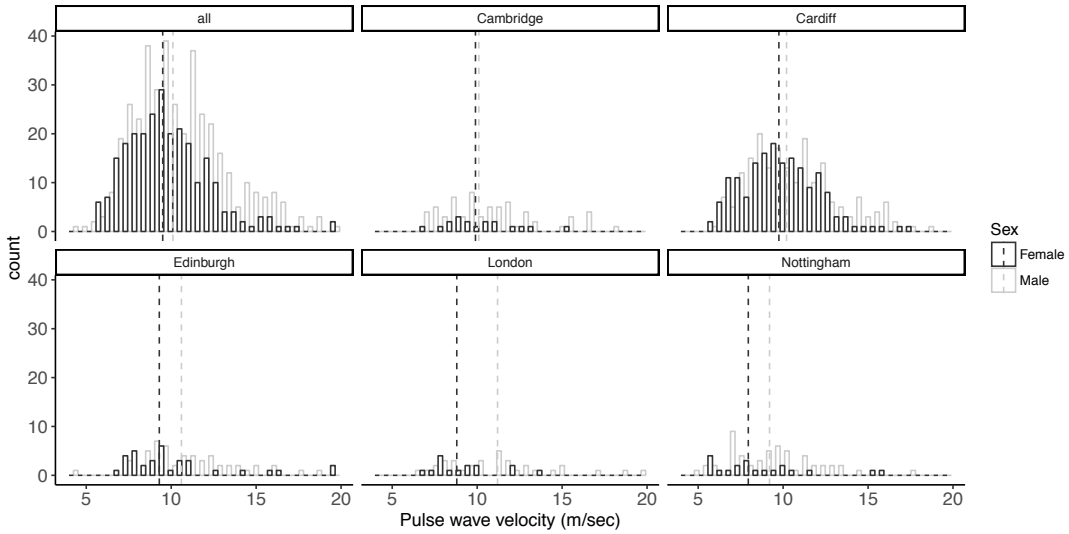

Figure 3 Differences in baseline pulse wave velocity.
Histograms displaying the distribution of PWV by sex and recruitment site. Dashed lines indicate median values by sex. Where only one median line is visible, medians for both sexes are similar.

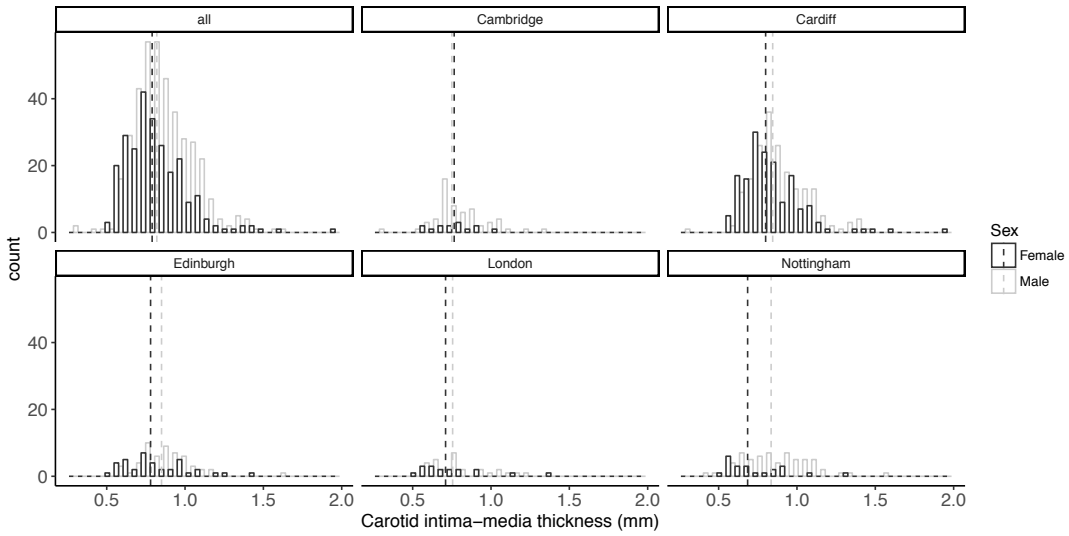

Figure 4 Differences in baseline carotid intima-media thickness.
Histograms displaying the distribution of CIMT by sex and recruitment site. Dashed lines indicate median values by sex. Where only one median line is visible, medians for both sexes are similar.

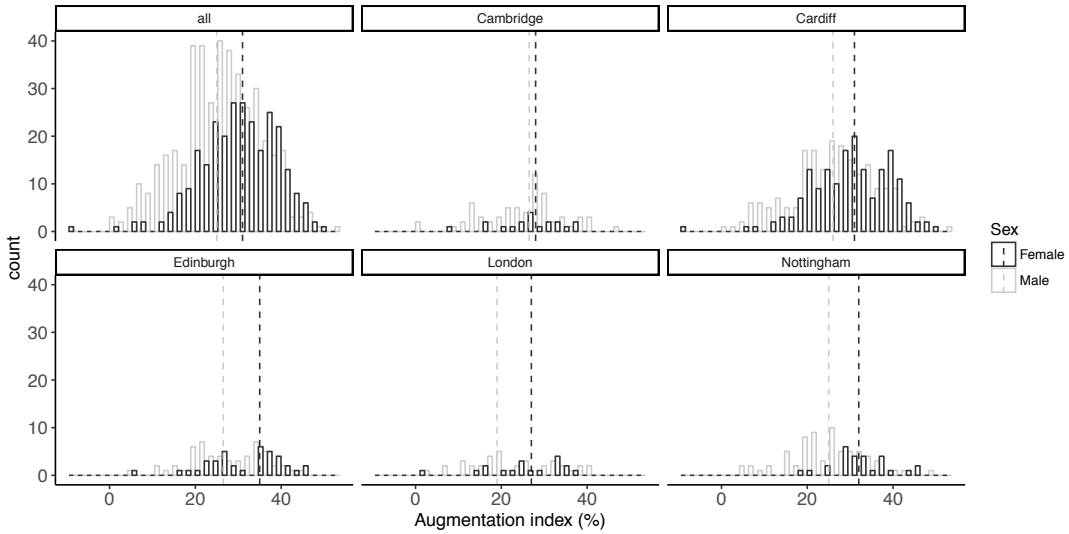

Figure 5 Differences in baseline augmentation index.
Histograms displaying the distribution of AIx by sex and recruitment site. Dashed lines indicate median values by sex.

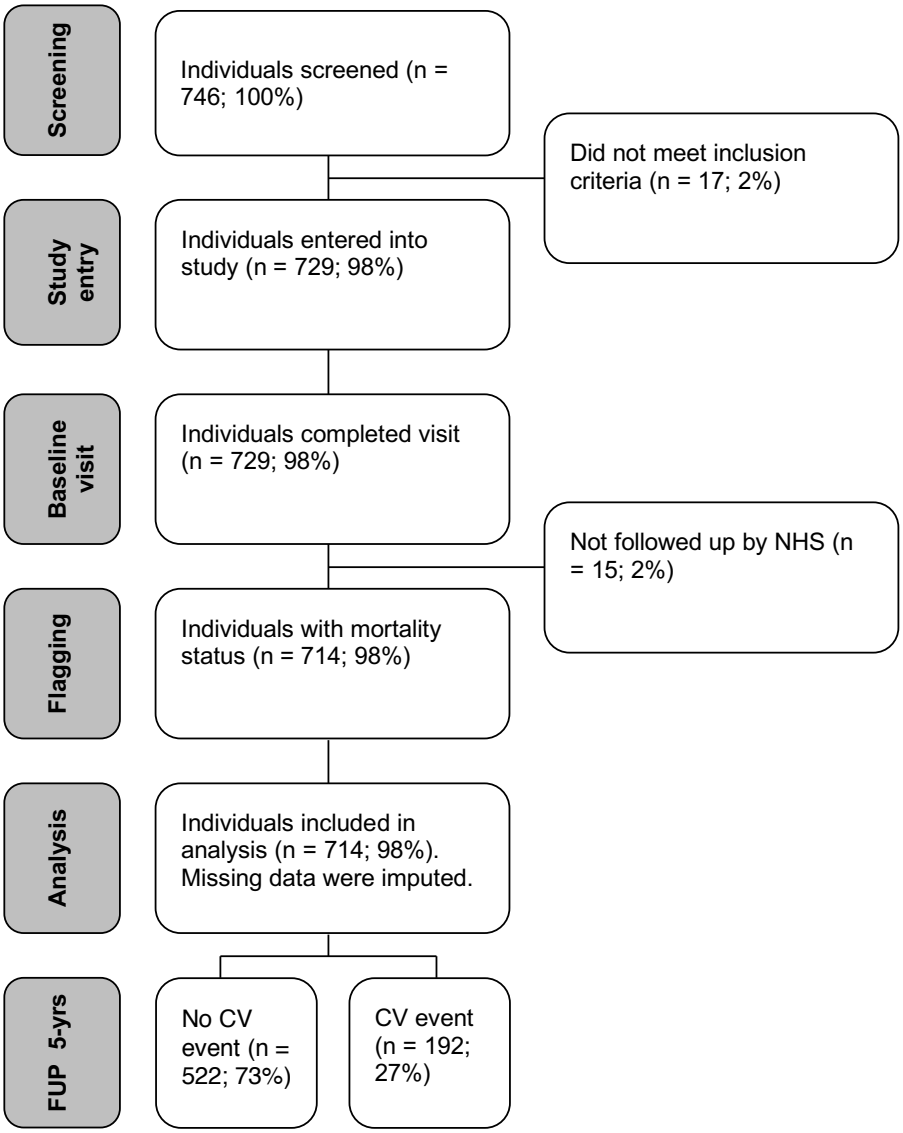

Figure 6 Participant enrolment flow diagram with five years follow up.

Total number of CV events (n = 192): peripheral arterial disease (n = 9), diseases of arteries, arterioles and capillaries (n = 7), angina (n = 21), unstable angina (n = 3), coronary heart disease not otherwise specified (n = 63), acute myocardial infarction (MI), and certain current complications following acute MI (n = 11), cerebral infarction (n = 11), stroke, not specified as haemorrhage or infarction (n = 3), other stroke (n = 18), heart failure (n = 32), abdominal aortic aneurysm (n = 8), and cardiac death (n = 6). FEV_1 = forced expiratory volume one second. FVC = forced vital capacity. NHS = National Health Services. FUP = follow-up period.